PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

EINGANG/RECEIVED
03. März 2005
Gewerbl. Rechtsschutz / Intellectual Property
ALTANA Pharma AG

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/053560	17.12.2004	19.12.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/454, A61P1/04, C07D491/14

Applicant
ALTANA PHARMA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Johnson, C Telephone No. +49 89 2399-8287

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/053560

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 16

because:

☒ the said international application, or the said claims Nos. 16 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

see separate sheet

III. Non-establishment of opinion

Claim 16 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V. Reasoned statement

Reference is made to the following documents:
D1: WO 03/014123
D2: WO 02/34749

Novelty

Although D1 mentions that the pure enantiomers of the compounds of formula 1 are the preferred subject matter of the invention (p. 6, 4th full paragraph), the (S)-enantiomer of the present invention is not directly and unambiguously disclosed in this document, and present claim 1 may be considered to be a novel selection from the disclosure of D1. The compounds of D2 differ from claim 1 because the pyran ring is substituted at the 4-position (i.e. one of R4a and R4b ≠ H).

Claims 1-16 fulfil the requirements of Article 33(2) PCT.

Inventive step

The technical problem underlying the present invention appears to be the provision of improved gastric acid secretion inhibitors. D1 may be considered the closest prior art. It has been shown that selected compounds of present claim 1 have an improved activity compared with their corresponding (R)-enantiomers (p. 79).

The question that must be answered is whether it is non-obvious that one enantiomer of a chiral compound has improved activity compared with the other or with the racemate. In decision T296/87 (OJ 1990, 195) the Technical Board of Appeal

discussed this question. Their conclusion was as follows (point 8.4.1): "*Long before the contested patent's priority date, it was generally known to specialists that, in physiologically active substances (e.g. herbicides, fungicides, insecticides and growth regulators, but also pharmaceuticals and foodstuffs) with an asymmetrical carbon atom enabling them to occur in the form of a racemate or one of two enantiomers, one of the latter frequently has a quantitatively greater effect than the other or than the racemate. If - as here - the aim is therefore to develop agents with increased physiological activity from a physiologically active racemate the obvious first step - before any thought is given, say, to synthesising structurally modified products - is to produce the two enantiomers in isolation and test whether one or the other is more active than the racemate. Such tests are routine. Under established Board case law, an enhanced effect cannot be adduced as evidence of an inventive step if it emerges from obvious tests.*"
In point 8.4.2 cases are given where the above generalisation cannot be applied. However, these cases do not appear to apply to the present application. Indeed, D2 (formula 1*, p. 38) shows that at the priority date of the present application it was known, not only in general, but also for structurally very similar compounds with the same biological activity, that one of the enantiomers, specifically the (S)-enantiomer, was preferred.

It would thus be obvious for the skilled person, with the common general knowledge that one enantiomer is often more active than the other or than the racemate (and with D2 showing that this generalisation is indeed applicable to gastric acid secretion inhibitors with the present tricyclic fused core), to solve the technical problem by providing the separate enantiomers and by testing them to ascertain which enantiomer has the higher activity.

Claims 1-16 therefore do not fulfil the requirements of Article 33(3) PCT.

Industrial applicability

Claims 1-15 fulfil the requirements of Article 33(4) PCT.

No unified criteria exist in the PCT Contracting States for assessing whether present

claim 16 is industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not consider claims to the use of a compound in medical treatment to be industrially applicable, but allows claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.